UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

19

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/583,117	05/15/00	STRAUS	D 50050/002001

HM12/1121

PAUL T CLARK
CLARK & ELBING LLP
176 FEDERAL STREET
BOSTON MA 02110

EXAMINER	
EINSMANN, J	
ART UNIT	**PAPER NUMBER**
1655	7

DATE MAILED: 11/21/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No.	Applicant(s)	
	09/333,110	STRAUS, DON	
	Examiner	Art Unit	
	Juliet C. Einsmann	1655	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 August 2000* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-60* is/are pending in the application.

4a) Of the above claim(s) *21-46 and 55-57* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-20,47-54 and 58-60* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. & 119(e).

Attachment(s)

15) ☐ Notice of References Cited (PTO-892)
16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *2 and 5* .
18) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
19) ☐ Notice of Informal Patent Application (PTO-152)
20) ☐ Other: .

DETAILED ACTION

1. This action is written in response applicant's correspondence submitted August 17, 2000, paper number 6. Claims 1, 4, 5, 7, 8, 11, 15-20, and 47 have been amended, and claims 58-60 have been added. Claims 1-60 are pending. Claims 21-46 and 55-57 are withdrawn from consideration as being drawn to a non-elected invention. Applicant's amendments and arguments have been thoroughly reviewed, but are not persuasive for the reasons that follow. Any rejections not reiterated in this action have been withdrawn as being obviated by the amendment of the claims. **This action is FINAL.**

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Specification- Sequence Rules

3. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821-1.825 because there is no sequence listing and no CRF has been submitted. See, for example, pages 73 and 78. Applicant is required to submit a CRF and paper copy of the Sequence Listing containing these sequences, an amendment directing the entry of the Sequence Listing into the specification, an amendment directing the insertion of the SEQ ID NOs into the appropriate pages of the specification and a letter stating that the content of the paper and computer readable copies are the same.

Claim Rejections - 35 USC § 112

4. Claims 52-54 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 52-54 are indefinite for the recitation of "the amplification products of step (a)(iv)" because step (a)(iv) refers to genomic representations, while step (a)(iii) refers to amplification products.

Response to Applicant's Remarks

This rejection was not addressed by applicant. Therefore it is reiterated.

Claim Rejections - 35 USC § 102

5. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

6. Claims 1-4, 8-14, 20, and 47-52 are rejected under 35 U.S.C. 102(e) as being anticipated by Shuber (US PAT 5834181).

Shuber teaches methods for obtaining genetic information from a biological sample comprising (a) providing a sample containing target nucleic acid molecules and (b) detecting the target molecules by contacting the sample with hybridization probes and identifying the

hybridized probes (abstract). Shuber specifically teaches that the method can be used with 10-200 probes, preferably allele specific oligonucleotides (Col. 7, lines 11-14). Shuber teaches multiple embodiments for his invention.

With respect to claims 4 and 11, Shuber teaches that it may be desirable to hybridize the polymers to the target in solution, i.e. without having bound the target to a support (Col. 6, line 66-Col. 7, line 4).

With respect to claims 8 and 14, Shuber further teaches that hybridized probes can be identified by the use of hybridization arrays, wherein members of the probe pool are separated from the target nucleic acids and re-hybridized to immobilized probes on an array (Col. 9, line 65-Col. 10, line 10). In this case, the method of Shuber comprises obtaining genetic information from a sample by (a) providing probes that hybridized to target nucleic acid molecules in a sample and (b) detecting the probes using an ensemble of probes, wherein the detection ensemble is immobilized on an array, wherein the probes of step (a) were obtained by first hybridizing a probe pool (ensemble of ID probes) with the sample and then separating them from the sample.

With respect to claim 10, Shuber teaches an embodiment in which the target nucleic acid is bound to a solid phase matrix (Col. 6, line 42-43).

With respect to claim 12, Shuber teaches that oligonucleotide probes can be synthesized to contain sequences complementary to the target region and additional pre-determined sequences that act as "tags" (Col. 10, lines 25-27).

With respect to claims 9 and 13 and 52, Shuber discloses in example 9 embodiment of the invention in which ligation based techniques are used (Col. 25, heading Example 9). In this case, probes that are intended to hybridize with the target are ligation probes and the ligation probes flank the site of a genetic alteration (Col. 26, lines 14-16). Shuber teaches that some probes which identify genetic alteration include ASO probes, which target small changes relative to the prevalent "wild type" sequence, including a single nucleotide (as in single nucleotide polymorphisms (SNP)) (Col. 4, lines 40-48). Shuber teaches that after ligation the ligated products can be amplified using LCR or PCR (Col. 26, lines 31-34), specifically teaching that one method for identification of ligated probes is to use the ligation product as a template for a linear amplification using a universal priming sequence (Col. 26, lines 63-66).

With respect to claims 50-51 in which greater than 20 or 50 probes must be used, note, as mentioned above, that Shuber teaches the methods of this invention can be used with 10-200 probes, preferably allele specific oligonucleotides (Col. 7, lines 11-14).

Response to Applicant's Remarks

Central to Applicant's arguments is the assertion that Shuber does not teach or obviate the two independent claims. Applicants arguments are not found persuasive for the reasons that follow.

Applicant argues that Shuber's primary focus is on the ability to scan numerous biological samples in parallel, while applicant's is on testing a single biological sample for the presence of distinct genomes or for numerous polymorphisms that occur throughout an entire genome. In response to applicant's argument that the references fail to show this feature, it is

noted that this feature is not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). Furthermore, Shuber specifically teaches that his methods "have the capacity to cost effectively analyze a large number of samples (>500) for a large number of mutations (>100) in a single assay (Col. 5, lines25-28)," and further specifies that the methods can be sued for the identification of multiple genes in a single patient's DNA sample, and that "the method is applicable when one or more genes or genetic loci are targets of interest (Col. 5, lines 54-57)." Thus, Shuber does in fact teach that his method can be used for the interrogation of unrelated sequences.

Applicant further argues that Shuber does not teach the use of a detection ensemble that has a minimum genomic derivation of 6 or more. However, in order to support this argument, applicant relies on an definition of "hybridizes to" found in the specification. This definition is not found in the claims, and is not considered to limit the claims since the term "hybridizes to" is a widely used term in the art and the broadest reasonable interpretation must be given to this phrase. The broadest interpretation would include the interpretation relied on in applicant's arguments, but would also include a more stringent hybridization conditions such as those used by Shuber. Shuber's intent is clearly to provide a set of probes which is able to distinguish between different possible alleles in a sample, and as such, the example provided by Shuber is considered to have a minimum genomic derivation of greater than five as the base claim requires.

With regard to claim 8, applicant argues that Shuber does not teach a step in which prior to step (a) nucleic acid molecules of the sample are hybridized with an ensemble of ID probes to

yield the probes of step (a)(ii). Shuber does in fact teach this limitation. Shuber teaches that two hybridization steps. First an ensemble is hybridized with the target nucleic acids (the sample). Then the members of the ensemble which hybridize with the sample are separated from the target nucleic acids, yielding the probes of step (a)(ii). Then, these probes are hybridized to the detection ensemble in order to determine the presence of the target nucleic acid in the sample. The method taught by Shuber does not differ from claim 8.

Applicant further argues that claim 8 requires hybridization to unpurified nucleic acids. This limitation is simply not found in claim 8.

7. Claims 1-4, 9, 11-15, 19-20, 47-48 and 52 are rejected under 35 U.S.C. 102(b) as being anticipated by Barany et al. (WO 97/31256).

Barany et al. teach a method for identifying a plurality of sequences differing by one or more single base changes, insertions, deletions or translocations in a plurality of target nucleotide sequences (abstract). The method comprises (a) providing a sample containing target nucleic acid molecules (p. 6, lines 13-15) (b) detecting the target nucleic acid molecules by means of a hybridization phase in which two probes suitable for ligation when hybridized adjacent to one another on a target nucleic acid are hybridized to a target molecule and ligated (p. 6, lines 25-30) and (c) identifying the nucleic acid molecule by means of a capture phase in which the probes are captured on an addressable array (p. 6, lines 35-40) and identity is determined based on their position on the array (p. 7, lines 3-7).

The method is exemplified in figure 8 wherein a single pair of amplification primers is used to amplify the region containing a mutation, and then a probe sets are used to detect

different mutations in two different codons. In this example there are twenty possible mutation combinations. Barany et al. teach that the probe ligation reactions are solution based (p. 48, lines 30-31), and one of each set of probes to be ligated comprises an oligonucleotide tag that will be useful for capture on the addressable array (p. 6, line 30). Barany et al. teach that this method is useful to determine the presence of viruses in a sample, including HIV, human T-cell lymphocytotrophic virus, hepatitis viruses, Epstein-Barr Virus, cytomegalovirus, human papillomaviruses, orthomyxo viruses, paramyxo viruses, adenoviruses, corona viruses, bunya viruses, and toga viruses (p. 21, lines 11-16).

Response to Applicant's Remarks

Applicant argues that the disclosure of Barany *et al.* suffers from the same deficiencies as Shuber. The arguments presented with regard to Shuber are therefore applied with regard to Barany *et al.* as well. Barany *et al.* clearly intend that their invention be used for the simultaneous detection of a wide array of nucleotide sequences. This assertion is supported by the Barany *et al.*'s claims 51-54 wherein they specify method is used to detect infectious diseases caused by bacterial, viral, parasitic, and fungal infectious agents, and they further list over fifty examples of such agents.

Claim Rejections - 35 USC § 103

8. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

9. Claims 7, 59, and 60 are rejected under 35 U.S.C. 103(a) as being unpatentable over Shuber in view of Bleiweiss et al. (J. of Reproductive Medicine, (Feb. 1992) 37(2) 151-156) or over Barany in view of Bleiweiss et al.

This rejection is reiterated for claim 7 and applied to newly added claims 59 and 60.

Shuber teaches methods for obtaining genetic information from a biological sample comprising (a) providing a sample containing target nucleic acid molecules and (b) detecting the target molecules by contacting the sample with hybridization probes and identifying the hybridized probes (abstract). Shuber specifically teaches that the method can be used with 10-200 probes, preferably allele specific oligonucleotides (Col. 7, lines 11-14).

Barany et al. teach a method for identifying a plurality of sequences differing by one or more single base changes, insertions, deletions or translocations in a plurality of target nucleotide sequences (abstract). The method comprises (a) providing a sample containing target nucleic acid molecules (p. 6, lines 13-15) (b) detecting the target nucleic acid molecules by means of a hybridization phase in which two probes suitable for ligation when hybridized adjacent to one another on a target nucleic acid are hybridized to a target molecule and ligated (p. 6, lines 25-30) and (c) identifying the nucleic acid molecule by means of a capture phase in which the probes are captured on an addressable array (p. 6, lines 35-40) and identity is determined based on their position on the array (p. 7, lines 3-7). The method is exemplified in figure 8 wherein a single pair of amplification primers is used to amplify the region containing a mutation, and then a probe sets are used to detect different mutations in two different codons. In this example there are twenty possible mutation combinations.

Neither Shuber nor Barany et al. teach the use of their method with *in situ* hybridization.

Bleiweiss et al. teach a method in which they identify human papillomavirus subtypes using in situ hybridization probes specific to recognize subtypes 6/11, 16/18, or 31/35/51 (p. 151-152). In the methods of Bleiweiss *et al.* the biological sample is treated to make nucleic acids available for hybridization without purifying said nucleic acid molecules from the sample.

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have used an in situ hybridization as taught by Bleiweiss et al. in method of Shuber or in the method of Barany et al. because Bleiweiss teaches that in situ hybridization has the advantage of extreme sensitivity, and is preferable over Southern blot assays because of "its preservation of cellular and nuclear morphology, allowing precise localization of a positive signal (p. 154)."

10. Claims 16-18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Shuber in view of Barany et al.

Shuber teaches methods for obtaining genetic information from a biological sample comprising (a) providing a sample containing target nucleic acid molecules and (b) detecting the target molecules by contacting the sample with hybridization probes and identifying the hybridized probes (abstract). Shuber specifically teaches that the method can be used with 10-200 probes, preferably allele specific oligonucleotides (Col. 7, lines 11-14). Shuber teaches multiple embodiments for his invention.

In one embodiment, Shuber teaches that the nucleic acid to be identified comprise bacteria and their phages, viruses, fungi and protozoa (Col. 6, lines 5-9). Shuber teaches that the

sample of nucleic acid can be isolated from a patient, particularly from any cell source or body fluid including blood cells, buccal cells, or tissue exudates at the site of infection (Col. 6, lines 13-23).

Shuber does not specifically identify any specific bacteria and their phages, viruses, fungi or protozoa that could be tested for in a nucleic acid sample.

Barany et al. teach a method for identifying a plurality of sequences differing by one or more single base changes, insertions, deletions or translocations in a plurality of target nucleotide sequences (abstract). Barany et al. teach that this method can be used to test for infectious diseases, including *Escherichia coli, Salmonella, Shigella, Pseudomonas, Mycobacterium tuberculosis, Mycobacterium avium-intracellulare, Yersinia, Staphylococcus aureus, Streptococcus pneumonia, Corynebacteria, Legionella, Mycoplasma, Chlamydia, Enterococcus faecalis, Cryptococcus neoformans, Blastomyces detmatitidis, Histoplasma capsulatum, Coccidioides immitis, Candida albicans, Entamoeba, and Necator americanis* (p. 20, line 33- p. 21, line 23).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have tested for the nucleic acids of the specific pathogens taught by Barany et al. in the method taught by Shuber since Shuber teaches that his method can be used for the identification specific nucleic acid sequences of "part of a foreign genetic sequence, e.g. the genome of an invading microrganism" including bacteria and their phages, viruses, fungi and protozoa (Col. 6, line6-7), and Barany et al. specifically list these bacteria and their phages, viruses, fungi and protozoa as pathogens that could be detected in a nucleic acid assay.

11. Claims 53 and 54 are rejected under 35 U.S.C. 103(a) as being unpatentable over Shuber in view of Jarnik et al. or as being unpatentable over Barany et al. in view of Jarnik et al.

Shuber teaches methods for obtaining genetic information from a biological sample comprising (a) providing a sample containing target nucleic acid molecules and (b) detecting the target molecules by contacting the sample with hybridization probes and identifying the hybridized probes (abstract). Shuber specifically teaches that the method can be used with 10-200 probes, preferably allele specific oligonucleotides (Col. 7, lines 11-14). Shuber discloses in example 9 embodiment of the invention in which ligation based techniques are used (Col. 25, heading Example 9). In this case, probes that are intended to hybridize with the target are ligation probes and the ligation probes flank the site of a genetic alteration (Col. 26, lines 14-16). Shuber teaches that some probes which identify gentetic alteration include ASO probes, which target small chages relative to the prevalent "wild type" sequence, including a single nucleotide (as in single nucleotide polymorphisms (SNP)) (Col. 4, lines 40-48). Shuber teaches that after ligation the ligated products can be amplified using LCR or PCR (Col. 26, lines 31-34), specifically teaching that one method for identification of ligated probes is to use the ligation product as a template for a linear amplification using a universal priming sequence (Col. 26, lines 63-66).

Barany et al. teach a method for identifying a plurality of sequences differing by one or more single base changes, insertions, deletions or translocations in a plurality of target nucleotide sequences (abstract). The method comprises (a) providing a sample containing target nucleic acid molecules (p. 6, lines 13-15) (b) detecting the target nucleic acid molecules by means of a

hybridization phase in which two probes suitable for ligation when hybridized adjacent to one another on a target nucleic acid are hybridized to a target molecule and ligated (p. 6, lines 25-30) and (c) identifying the nucleic acid molecule by means of a capture phase in which the probes are captured on an addressable array (p. 6, lines 35-40) and identity is determined based on their position on the array (p. 7, lines 3-7). The method is exemplified in figure 8 wherein a single pair of amplification primers is used to amplify the region containing a mutation, and then a probe sets are used to detect different mutations in two different codons. In this example there are twenty possible mutation combinations.

Neither Shuber nor Barany teach the use of this method wherein amplification sequences are used to direct the amplification of sequences lying between Alu repeats using Alu-specific primers.

Jarnik et al. teach a method which comprises using inter-Alu PCR and using the PCR products as probes (p. 389, Col. 1) for the detection of genomic rearrangements and/or deletions in cancer cells.

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have used inter-Alu PCR and Alu probes in the method of Shuber or in the method of Barany et al. in order to have produced a method useful for detecting genomic rearrangements and/or deletions in cancer cells, or for other types of cancer detection methods since Jarnik et al. teach "In addition to the detection of LOH, inter-Alu PCR typing systems also detect genomic instabilities occurring in certain hereditary as well as in a fraction of sporadic cancer cells (p. 397)."

Response to Applicant's Remarks

Applicant's remarks concerning the 103 rejections relied on the arguments concerning the deficiencies of the Shuber and Barany *et al.* references. These arguments have been addressed above.

NEW GROUNDS OF REJECTION AND OBJECTION NECESSITATED BY APPLICANT'S AMENDMENT OF THE CLAIMS

Claim Rejections - 35 USC § 112

12. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 59-60 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. MPEP 2163.06 notes "If new matter is added to the claims, the examiner should reject the claims under 35 U.S.C. 112, first paragraph - written description requirement. In re Rasmussen , 650 F.2d 1212, 211 USPQ 323 (CCPA 1981)."

In the instantly rejected claims, the new limitation of "without purifying said nucleic acid molecules from said sample" in claims 59 and 60 appears to represent new matter. No specific basis for this limitation was identified in the specification, nor did a review of the specification

by the examiner find any basis for the limitation. Specifically, the exclusion proviso in which "without purifying" is required is not found in the specification. As noted by MPEP 2173.05(i),

> "Any negative limitation or exclusionary proviso must have basis in the original disclosure. See Ex parte Grasselli , 231 USPQ 393 (Bd. App. 1983) aff'd mem., 738 F.2d 453 (Fed. Cir. 1984). The mere absence of a positive recitation is not basis for an exclusion. Any claim containing a negative limitation which does not have basis in the original disclosure should be rejected under 35 U.S.C. 112, first paragraph as failing to comply with the written description requirement."

Since no basis has been identified, the claims are rejected as incorporating new matter.

13. Claims 5-7, 16-19 and 47 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 5 and 6 are indefinite because it is unclear how the amplified probes are used in the method of the base claim. Step b) of the base claim indicates that it is a hybridization step of the nucleic acid molecules of step (a) with the detection ensemble. If the amplified probes are intended to be the amplification products of step (a)(iii) then the claim should be amended to clarify this point.

Claim 7 is indefinite over the amendment which indicates that the *in situ* hybridization should occur "following step (b)." In step (b) the target nucleic acid molecules are detected, and so it is unclear what exactly is being hybridized in the *in situ* hybridization step. The current claim reads directs that the detection of the target nucleic acid occurs, and after that a quantification by *in situ* hybridization occurs. If it is Applicant's intent that the detection step of (b) occur *in situ*, this is not clear.

Claims 16-19 are indefinite over the recitation of "comprise 6 or more different nucleic acid molecules from" because it is not clear if the intention of the claim is that there be 6 or more different nucleic acid molecules from different parts of each of the organisms recited OR if there should be nucleic acids which represent 6 or more of the different organisms recited. It appears that improper Markush language is being used in this claim.

Claim 47 is indefinite because it is not complete. The amended claim ends with step (b), and does not end with a period.

Claim Rejections - 35 USC § 103

14. Claims 5, 6, and 58 are rejected under 35 U.S.C. 103(a) as being unpatentable over Shuber in view of Straus *et al.* (PNAS USA Vol. 87, pp. 1889-1893, March 1990).

Shuber teaches methods for obtaining genetic information from a biological sample comprising (a) providing a sample containing target nucleic acid molecules and (b) detecting the target molecules by contacting the sample with hybridization probes and identifying the hybridized probes (abstract). Shuber specifically teaches that the method can be used with 10-200 probes, preferably allele specific oligonucleotides (Col. 7, lines 11-14). Shuber teaches multiple embodiments for his invention.

With respect to claims 8 and 14, Shuber further teaches that hybridized probes can be identified by the use of hybridization arrays, wherein members of the probe pool are separated from the target nucleic acids and re-hybridized to immobilized probes on an array (Col. 9, line 65-Col. 10, line 10). In this case, the method of Shuber comprises obtaining genetic information from a sample by (a) providing probes that hybridized to target nucleic acid molecules in a

sample and (b) detecting the probes using an ensemble of probes, wherein the detection ensemble is immobilized on an array, wherein the probes of step (a) were obtained by first hybridizing a probe pool (ensemble of ID probes) with the sample and then separating them from the sample.

Shuber further discloses in example 9 embodiment of the invention in which ligation based techniques are used (Col. 25, heading Example 9). In this case, probes that are intended to hybridize with the target are ligation probes and the ligation probes flank the site of a genetic alteration (Col. 26, lines 14-16). Shuber teaches that some probes which identify genetic alteration include ASO probes, which target small changes relative to the prevalent "wild type" sequence, including a single nucleotide (as in single nucleotide polymorphisms (SNP)) (Col. 4, lines 40-48). Shuber teaches that after ligation the ligated products can be amplified using LCR or PCR (Col. 26, lines 31-34), specifically teaching that one method for identification of ligated probes is to use the ligation product as a template for a linear amplification using a universal priming sequence (Col. 26, lines 63-66).

Shuber does not specifically exemplify the universal priming sequences.

Straus *et al.* teach the use of adapters on the end of probes that allow amplification of a wide variety of sequences using a single primer pair (p. 1890). It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have used adapters such as those taught by Straus *et al.* in the methods taught by Shuber since Shuber suggests using a universal priming sequence and Straus teaches such a sequence. Furthermore, Straus *et al.* motivate the use of such primers when they point out that "Amplification of the

remaining DNA, using the PCR provides enough DNA to proceed with the experiment. The PCR requires that template molecules be flanked by defined sequences that can hybridize oligonucleotide primers (p. 1891)."

Conclusion

15. No claims are allowed.

16. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Juliet C. Einsmann whose telephone number is (703) 306-5824. The examiner can normally be reached on Monday through Thursday, 7:00 AM to 4:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, W. Gary Jones can be reached on (703) 308-1152. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 and (703) 305-3014.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

JEFFREY FREDMAN
PRIMARY EXAMINER

Juliet C. Einsmann
Examiner
Art Unit 1655

November 20, 2000